REMARKS

Status of Claims

Claims 1-3, 5-11, and 21-59 are pending in this application and were examined. Claims 12-13 are pending but were withdrawn from consideration as being drawn to non-elected inventions.

This paper amends claims 1, 3, 5, and 34. Claims 1-3, 5-11, and 21-59 are currently under examination.

The Office Action

Claims 3, 5-12, and 21-43 stand rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. Claims 1-3, 5-11, and 21-59 stand rejected under 35 U.S.C. § 103 as obvious over Hafez et al. (*Biophysical Journal*, 79: 1438-1446, 2000; "Hafez") in view of Huang (U.S. Patent 5,283,122; "Huang") or Lishko et al. (U.S. Patent 5,753,263; "Lishko"). Claims 1-3, 5-11, and 21-59 stand rejected under 35 U.S.C. § 103(a) as obvious over Deshmukh et al. (U.S. Patent 6,258,792; "Deshmukh") alone or, in the alternative, over Hafez in view of Deshmukh.

Support for Amendments

Support for the amendment to claims 1 and 3 is found throughout the specification, but particular note is made of page 11, lines 11-16 and Example 9 (p. 23).

The remaining amendments to claims 1, 3, 5, and 34 are minor grammatical corrections. Support is found generally throughout the specification.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 3, 5-12, and 21-43 stand rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. Each ground of rejection is addressed individually below.

The Examiner asserts that claim 3 is indefinite because it is not further limiting with respect to claim 1. Applicants point out that claim 3 is independent (i.e., does not depend from claim 1) so, as a preliminary matter, is not necessarily required to be narrower in scope.

Claim 3 has a different scope than claim 1. The liposome of claim 1 must comprise at least two different amphipatic lipids; one with a positive charge and one with a negative charge. In contrast, the liposome of claim 3 must comprise at least one amphipatic lipid, where that single lipid has both a positive charge and a negative charge. In sum, claims 1 and 3 are unrelated and have a different scope.

Claim 5 is amended to clarify that the amphipatic molecule is an amphipatic lipid.

Claim 1 is amended to correct the antecedent basis of claims 23, 33, and 39.

All indefiniteness rejections are traversed and should be withdrawn. Such action is respectfully requested.

Rejections Under 35 U.S.C. § 103

I. The Claimed Invention

The invention, as currently claimed, is an amphoteric liposome that contains an anionic lipid, a cationic lipid, and a neutral lipid that is stable both at a low pH and a neutral pH. Specifically, Applicants have described a novel liposome that is stable and may be loaded with active ingredients, such as nucleic acids, at a low pH and then may be transitioned to a higher (i.e., neutral pH) for washing and storage. Specification at p. 11, ll. 11-16. As noted at page 8 of the Specification, the amphoteric nature of the liposomes is important because cationic liposomes are fusogenic and useful for transporting active ingredients into cells, but anionic liposomes are more stable and compatible with blood and serum components. This allows therapeutic administration of the anionic liposomes (i.e., do not aggregate immediately upon intravenous administration). Specification at p. 14, first and second paragraphs, and pp. 18-19

(Examples 4-5). But, the ability to acquire a positive charge at a low pH allows for effective loading of polyanionic therapeutic agents such as nucleic acids. Specification at pp. 20-22 (Examples 6-8). These properties allow for liposomal preparation and loading at low pH, followed by a rapid pH transition through the fusogenic pH zone into the more stable neutral pH zone for storage and administration.

II. Applicable Legal Standard For Obviousness

In order to make a *prima facie* case of obviousness, the Examiner must demonstrate that the prior art (i) teaches or suggests every claim limitation, (ii) provides a motivation to combine (or modify) the teachings of the selected references, and (iii) provides a reasonable expectation of success. M.P.E.P. § 2143.

The Examiner must demonstrate that the prior art specifically provides a motivation to combine the teachings of the selected references. The fact that the modification of the prior art to arrive at the claimed invention is within the capabilities of the skilled artisan in not sufficient by itself to provide a motivation to combine references. In re Kotzab, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000); Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

It is well established that prior art references are not properly combined, and fail to establish a *prima facie* case of obviousness, if their combination or modification renders the device inoperable for its intended purpose. In re Gordon, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984) (not obvious to turn the prior art device upside down because it would render the device inoperable); Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991).

In order to avoid the inappropriate use of a hindsight analysis, the courts have repeatedly cautioned that the teaching or suggestion to make the claimed combination must be found in the prior art, not in applicant's disclosure. See, In re Dembiczak, 175 F.3d 944, 50 USPQ2d 1614 (Fed. Cir. 1999). "It is impermissible to first ascertain factually what [applicants] did and then

view the prior art in such a manner as to select from the random facts of art only those which may be modified and then utilized to reconstruct appellants invention from such prior art." Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985).

III. Rejection over Hafez in View of Huang and Lishko

Claims 1-3, 5-11, and 21-59 stand rejected under 35 U.S.C. § 103(a) as obvious over Hafez in view of either Huang or Lishko. Specifically, the Examiner asserts that Hafez teaches liposomes, containing CHEMS (an anionic lipid) and DODAC (a cationic lipid), that have a pH_f 4.0 to 6.7, but lacking the inclusion of a neutral lipid such as cholesterol or phosphatidylcholine (PC). The Examiner further asserts that Huang discloses that the inclusion of cholesterol into pH-sensitive liposomes reduces the leakage of liposomal contents and that Lishko discloses the inclusion of PC or cholesterol into pH-sensitive liposomes. The Examiner concludes, therefore, that it is obvious to modify the pH-sensitive liposomes of Hafez by adding a neutral lipid, as taught by either Huang or Lishko, to arrive at the claimed invention. Applicants respectfully disagree.

A. The Deficiency of Hafez

The liposomes of the present invention are fundamentally different from those of Hafez. As discussed above, the liposomes, as currently claimed, are stable enough at a low pH that they are capable of being loaded with polyanions such as nucleic acids and are also stable at a neutral pH. By contrast, the CHEMS/DODAC liposomes of Hafez are designed to be increasingly fusogenic as the pH is lowered (see Figures 2A and 3). The other type of Hafez liposomes—DOPA/DC-Chol—were prepared (and stable) at a low pH, but became increasingly fusogenic as the pH was raised (see Figure 4A). The CHEMS/DODAC liposomes may be useful for storage and administration, like the present liposomes, but they are not easily loaded with anionic therapeutics. The DOPA/DC-Chol liposomes may be loaded with anionic therapeutics when made at a low pH, are not easily stored or administered at a neutral pH. Nowhere does Hafez teach or suggest how to modify the liposomes to be stable both at a low pH and a neutral pH; nor does Hafez even suggest that such a liposome would be desirable. Thus, the Hafez liposomes have substantially different properties than those of the present invention.

B. Huang and Lishko Do Not Provide What Hafez Lacks

Neither Huang nor Lishko provide what Hafez lacks. Huang discloses liposome having mixtures of anionic and neutral lipids. These liposomes, like those of Hafez, become increasingly fusogenic as the pH is lowered (see, for example Figure 2 with col. 5, ll. 22-26, and Figure 3 with col. 5, ll. 40-50). Huang provides no instruction on how to make a liposome that is stable both at a low pH and an neutral pH. Specifically, Huang teaches how to avoid leakage of the liposomal contents during fusion. Likewise, Lishko teaches liposomal formulations of anionic and neutral lipids. The Lishko liposomes comprise one or more of PC, EPC, DOPC, DPPC, PE, DOPE and cholesterol, combined with one or more phospholipid to form a pH-sensitive liposome (col. 15, ll. 13-17). However, all of the combinations suggested by Lishko would be unstable at a low pH. There is nothing in Lishko to teach or suggest to the artisan the desirability or the methodology for making a liposome that is stable at a low pH. Therefore, nothing in either Huang or Lishko teaches the artisan how to make an amphoteric liposome that is stable at a low pH. Thus, the combination of Huang or Lishko with Hafez does not result in the instant invention. Accordingly, this rejection should be withdrawn and such action is respectfully requested.

IV. Rejection over Deshmukh

Claims 1-3, 5-11, and 21-59 stand rejected under 35 U.S.C. § 103(a) as obvious over Deshmukh. Specifically, the Examiner states that Deshmukh teaches cationic liposomes having a cationic, an anionic, and a neutral lipid. Office Action at p. 6, ll. 2-3. The Examiner asserts that an artisan is motivated, based on the teachings of Deshmukh, to vary the amounts of cationic and anionic lipids to obtain a liposome with the desired net positive or negative charge at physiological pH, depending upon the use of the liposome to arrive at the presently claimed invention. Office Action at p. 6, ll. 11-14. Applicants respectfully disagree and submit that the Examiner has failed in several aspects to make a *prima facie* case of obviousness.

A. Deshmukh Does Not Teach or Suggest Amphoteric Liposomes

The Examiner correctly characterizes Deshmukh by stating that, "[a]ccording to Deshmukh, the negatively charged lipid can be included so long as the net charge of the complexes form is positive." Office Action at p. 6, ll. 2-3 (emphasis added). The Examiner incorrectly asserts that, based on Deshmukh, the artisan "would be motivated to vary the amounts of the cationic lipid and the anionic lipid as in instant claims to obtain a liposome with desired net positive or negative charge at physiological pH." Office Action at p. 6 ,ll. 11-14.

Nothing in Deshmukh teaches or suggests making a liposome having a negative charge at physiological pH. The assertion to the contrary by the Examiner is unsupported by Deshmukh.

Deshmukh teaches liposomes that are cationic because the preferred biologically active substances disclosed in Deshmukh are negatively charged (e.g., nucleic acids, negatively charged proteins, carbohydrates including polysaccharides, and negatively charged drugs). Deshmukh at col. 8, ll. 48-51. In order to facilitate loading and/or adherence of the negatively charged active substances into/onto the Deshmukh liposomes, the Deshmukh liposomes must be cationic. Consequently, Deshmukh limits itself actively to cationic lipid mixtures, even if anionic lipids are present. Furthermore, Deshmukh cannot motivate the artisan to make liposomes that have a negative charge at physiological pH because it would make loading of the negatively charged active ingredients difficult or impossible. For these reasons, Deshmukh cannot render obvious the presently claimed invention. This rejection should be withdrawn and such action is respectfully requested.

B. Deshmukh Does Not Teach or Suggest the Use of Amphoteric Lipids

Claims 3, 5, and 6 are not rendered obvious by Deshmukh. Claim 3 (from which claims 5 and 6 depend) requires that the amphoteric liposomes contain a lipid that carries both a positive and a negative charge (i.e., are amphoteric). Nowhere does Deshmukh teach or suggest using these amphoteric lipids in the preparation of liposomes. Accordingly, Deshmukh does not render claims 3, 5, and 6 obvious. This rejection should be withdrawn and such action is respectfully requested.

Applicants respectfully submit that this rejection is traversed by the present claim amendments and clarification of the Deshmukh specification. This rejection may be withdrawn.

V. Rejection over Hafez in view of Deshmukh

Claims 5-11 and 22 stand rejected under 35 U.S.C. § 103(a) as obvious over Hafez in view of Deshmukh. The Examiner applies Hafez as discussed above (i.e., as disclosing liposomes containing cationic and anionic lipids). The Examiner notes that Hafez lacks a teaching to include a neutral lipid and an active agent. The Examiner asserts that it would have been obvious to combine the teachings of Hafez with that of Deshmukh as described above (i.e., to include a neutral lipid and an active agent such as DNA, RNA, or proteins) to arrive at the presently claimed invention. Applicants respectfully traverse.

A. Hafez and Deshmukh Cannot Properly Be Combined

The teachings of Hafez and Deshmukh cannot be properly combined because these references have different requirements that are mutually exclusive. Hafez teaches the creation of liposomes having a pH_f of 4 – 6.7 (i.e., that are anionic at physiological pH). Deshmukh requires cationic liposomes (col. 7, lines. 33-35 and col. 7, lines. 46-51). It is impossible for a liposome to be simultaneously anionic (satisfying Hafez) and cationic (satisfying Deshmukh) at physiological pH. The mutually exclusive requirements of these two references, therefore, renders the combination of references improper because there is no motivation to combine the otherwise incompatible teachings. The Examiner is "cherry-picking" the prior art for claim elements irrespective of their context. The Examiner improperly combines the teachings of two incompatible and mutually exclusive liposomal formulations in order to arrive at, what is asserted to be, the claimed invention. This is the type of hindsight analysis that the Federal Circuit strongly cautions against.

The Examiner further attempts to bolster this combination of prior art by stating that "the neutral lipid suggested by Deshmukh does not contribute any charge at all at the physiological

pH." The Examiner's own statement—that neutral lipids do not contribute to the overall charge of the liposome—argues against combining Hafez and Deshmukh. If the sole concern in liposomal formulation was the overall charge, there would be no motivation to add a neutral lipid. By contrast, Applicants have surprisingly discovered that the addition of a neutral lipid, although not contributing any charge at all at the physiological pH, has a substantial impact on the particle stability at low pH.

Accordingly, in view of the present claim amendments and foregoing arguments, Applicants submit that the combination of Hafez and Deshmukh does not render the instant invention obvious. This rejection should be withdrawn and such action is respectfully requested.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If the Examiner should have any questions concerning this communication or feels that an interview would be helpful to expedite allowance of this case, the Examiner is requested to call Applicants' undersigned attorney.

Respectfully submitted,

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